

Food and Drug Administration  
Rockville MD 20857

OCT 19 1999

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Fung Lam, M.D.  
Terbutaline Strategy Group  
3838 California Street, #812  
San Francisco, California 94118

Re: Docket No. 98P-0218/CP1

Dear Dr. Lam:

This is in response to your citizen petition (Petition) submitted on April 7, 1998, on behalf of the Terbutaline Strategy Group. In your petition, you request that the Food and Drug Administration (FDA) acknowledge subcutaneous terbutaline as a drug for professional use in the treatment of preterm labor and that FDA reevaluate the position taken in its November 13, 1997, "Dear Colleague" letter on the use of subcutaneous terbutaline to manage preterm labor. You also request that FDA take the following actions: (1) Notify the organizations who received the "Dear Colleague" letter that the use of terbutaline in managing preterm labor is as safe and effective as ritodrine and that the deaths of patients receiving terbutaline were not due to the drug; (2) ask manufacturers of terbutaline sulfate to remove package insert statements about the use of terbutaline in managing preterm labor and to submit data to the Agency to obtain approval for the use of terbutaline for this indication; and (3) expedite the review of any pending applications for approval of drugs for tocolysis.

FDA reaffirms the position stated in the "Dear Colleague" letter that there is no evidence of the effectiveness of prolonged treatment with subcutaneous terbutaline to manage preterm labor and that there are significant safety concerns associated with unmonitored, long-term administration of the drug. Consequently, to the extent that your petition requests that FDA change this position, your request is denied. Similarly, FDA denies your request that the Agency notify recipients of the "Dear Colleague" letter that terbutaline is as safe and effective as ritodrine for managing preterm labor and that terbutaline has not caused any deaths. In addition, although FDA has talked with the manufacturers of terbutaline to address the need for clarification of the uses and risks of terbutaline, the Agency has no basis at this time to require terbutaline manufacturers to remove statements about tocolysis from existing package inserts. Finally, FDA has already invited terbutaline manufacturers to submit supplemental new drug applications (NDAs) for approval of a tocolytic indication for terbutaline. If any such application is submitted, the Agency will strongly consider granting it priority review status.

#### I. ISSUES RAISED IN THE PETITION

You discuss several grounds for your request for FDA action regarding subcutaneous terbutaline. A listing of those grounds and the Agency's responses to them follows.

98P-0218

PDN 1

**A. Severity of the Problem of Premature Births in the United States**

You contend that by allegedly intervening in the practice of medicine and limiting treatment options, FDA is ignoring the severity of the problem of premature birth in the United States (Petition at 2). You state that preterm delivery occurs in 6 to 8 percent of pregnancies in the United States and that the complications of prematurity account for more than 60 percent of perinatal mortality (*id.*). You also state that attempts at tocolysis are made to prolong pregnancy in the hope of avoiding the morbidity and mortality associated with prematurity, and that delaying delivery can also allow time for an in utero transfer, thus enabling a premature infant to be delivered in an obstetric unit with neonatal intensive care facilities. You note that the drugs most commonly used in this country to treat preterm labor are the beta-mimetic agents ritodrine and terbutaline as well as magnesium sulfate, adding that only ritodrine for intravenous administration is approved by FDA for such use (*id.* at 3).

FDA agrees that premature birth is a serious healthcare problem in this country. The Agency has been deeply involved in efforts to address the problem. Through its advisory committees dealing with fertility matters, FDA has long provided a public forum in which data supporting the safe and effective use of tocolytics can be debated and disseminated. In 1992, the Fertility and Maternal Health Advisory Committee reviewed the data available on oral ritodrine maintenance therapy for tocolysis and concluded that ritodrine was not effective for tocolytic maintenance. In 1993, the advisory committee reviewed the literature on the safety and efficacy of terbutaline for treating preterm labor even though no application for approval was pending before FDA. The committee concluded that terbutaline administered intravenously appeared to have an acceptable risk-benefit profile for the acute treatment of preterm labor under limited circumstances (i.e., in pregnancies of 33 weeks or less, when cervical dilation is 4 centimeters or less and there is no premature rupture of the membranes, and with careful maternal and fetal monitoring).<sup>1</sup> Pursuant to a recommendation by the committee, FDA invited the sponsors of approved terbutaline drug products to submit supplemental NDAs for tocolysis. FDA also encouraged terbutaline sponsors to review their product labeling to address the need for clarification and characterization of the uses and risks of terbutaline. Most recently, the Reproductive Health Drugs Advisory Committee reviewed an NDA for the tocolytic atosiban in April 1998. At FDA's request, the advisory committee made recommendations regarding appropriate clinical trial endpoints for further clinical studies on atosiban.

FDA denies your contention that the Agency has intervened in the practice of medicine regarding the prevention of preterm birth. FDA has taken no action that would prohibit the use of any form of terbutaline by physicians in the practice of medicine, including treating preterm labor. However, Federal law requires the Agency to ensure that prescription drugs are safe and effective for the uses for which they are marketed and promoted. There is no approved application for the

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<sup>1</sup>Transcript of Fertility and Maternal Health Drugs Advisory Committee meeting, May 21, 1993, at 181-183.

use of terbutaline — by any route of administration — as a tocolytic agent, despite active promotion of subcutaneously administered terbutaline for such use by some commercial parties.

Moreover, practicing physicians and the public rely on FDA to continue to monitor the safety and effectiveness of marketed drugs, and the Agency has a responsibility to provide medical practitioners with the best information available to make sound therapeutic decisions. It is important that physicians who treat preterm labor be fully aware that, despite commercial promotion of subcutaneous terbutaline, there are no controlled studies that establish the safety and effectiveness of prolonged administration of subcutaneous terbutaline in treating preterm labor beyond 48 to 72 hours. This is especially important because subcutaneous terbutaline is often provided under conditions, such as prolonged outpatient administration, that do not afford the maternal and fetal monitoring appropriate for the drug's known toxicity profile.

## **B. Clinical Efficacy and Safety of Terbutaline as a Tocolytic**

### **1. Efficacy**

You describe numerous articles from the medical literature that you believe support the efficacy of beta-agonist agents as tocolytics. FDA has previously reviewed each of the articles that you cite. None of these articles contains data demonstrating a long-term tocolytic benefit (i.e., beyond 48 to 72 hours) for terbutaline or any other beta-agonist. Further, other than providing a brief opportunity for administration of maternal glucocorticoids or transfer to a tertiary care facility, the data do not support any measurable infant benefit from treatment with beta-agonist tocolytics.<sup>2</sup> There is no conclusive evidence that the use of terbutaline by any method of administration produces consistent benefits in gestational age at delivery, birth weight, neonatal morbidity, or perinatal morbidity. In fact, most studies offer evidence suggesting that there are no such benefits.

Despite having been studied in randomized, controlled clinical trials, *oral* dosage forms of beta-sympathomimetic tocolytics, including terbutaline, have not been shown to contribute to the prolongation of pregnancy. It is not known whether this lack of efficacy is due to the clinical pharmacology of orally dosed beta-agonists, to tachyphylaxis related to prolonged administration, or to other factors. Lack of efficacy in the presence of known toxicity was the reason that the FDA Fertility and Maternal Health Advisory Committee concluded in 1992 that oral ritodrine had no place in obstetric practice. The published literature clearly suggests that oral terbutaline is similarly ineffective as a pregnancy maintenance treatment. But because oral terbutaline is

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<sup>2</sup>Canadian Preterm Labor Investigators Group, "Treatment of Preterm Labor With the Beta-Adrenergic Agonist Ritodrine," *New England Journal of Medicine*, 327:308-312, 1992; J.F. King et al., "Beta-Mimetics in Preterm Labour: An Overview of the Randomized Clinical Trials," *British Journal of Obstetrics and Gynecology*, 95:211-212, 1988.

marketed for a pulmonary indication, it is available for physicians who wish to prescribe it as a tocolytic. However, oral terbutaline has never been promoted for tocolytic use by its manufacturers or others.

The published literature on the effectiveness of terbutaline administered *subcutaneously* to manage preterm labor is confined to observational studies, generally without the benefit of randomization or controls. Those studies that are controlled are either very small, therefore lacking the statistical strength to support any conclusion, or are published only in abstract form. The importance of having well-controlled clinical trials to confirm the effectiveness of a drug to treat preterm labor is magnified by the fact that there is little consistency in the definition or usage of the term "preterm labor" in the medical literature on tocolytics. Moreover, certain inclusion criteria frequently used in such studies — uterine contractions and cervical change — are often seen in women who eventually deliver at term without medical intervention. In many of the reported studies, most women with a diagnosis of preterm labor who were assigned to placebo or no-treatment groups eventually delivered at or near term. Therefore, the use of contemporaneous, randomly assigned control groups is needed to properly assess the effectiveness of a particular tocolytic.

Following are comments on the studies you reference (Petition at 11-13, 17-18) concerning the effectiveness of subcutaneous terbutaline that have been reported since the May 1993 advisory committee meeting:

- (1) Allbert et al. examined the efficacy of subcutaneous terbutaline in 992 women and reported that pregnancy was prolonged an average of 7 weeks (with treated patients delivering, on average, at 36 weeks' gestation).<sup>3</sup> This study is a retrospective record review, and the authors do not describe how records were selected. Further, the only eligibility criterion for treatment was any magnitude of cervical change, putting patients at variable risk for preterm delivery.
- (2) The study by Elliott et al. of terbutaline administered via subcutaneous infusion pump is a nonrandomized, noncomparative observational study of use of the drug in high-order multiple gestations.<sup>4</sup>
- (3) The study by Perry et al. is a retrospective chart review, much like that of Allbert et al. As in the Allbert study, the authors do not clearly specify their

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<sup>3</sup>J.R. Allbert et al., "Tocolysis for Recurrent Preterm Labor Using a Continuous Subcutaneous Infusion Pump," *Journal of Reproductive Medicine*, 39:614-618, 1994.

<sup>4</sup>J.P. Elliot et al., "Terbutaline Pump Tocolysis in High-Order Multiple Gestation," *Journal of Reproductive Medicine*, 42:687-694, 1997.

criteria for chart selection, a major potential bias in the ascertainment of outcomes.<sup>5</sup>

Only two of the studies you cite involve controlled trials of subcutaneously administered terbutaline for tocolysis. One is an abstract; the other is a very small study with equivocal results:

- (1) A study by Wenstrom et al. randomized patients with protocol-defined progressive cervical change to terbutaline by subcutaneous pump (blinded), saline by subcutaneous pump (blinded), or oral terbutaline once preterm labor was arrested with intravenous magnesium.<sup>6</sup> In all, 42 patients were randomized, and the mean gestational age at delivery and neonatal outcomes were the same in all three groups. This study is very small, and while the authors conclude that the three maintenance treatment arms appear equivalent, the statistical strength of that equivalence is not robust and conclusions are difficult to reach. Interestingly, however, the authors conclude that the terbutaline pump should remain experimental.
- (2) An abstract of a study by Lam et al., presented at the Society of Perinatal Obstetrics annual meeting in January 1998, describes a trial in which 256 patients who failed oral terbutaline received subcutaneous terbutaline and subsequently experienced prolonged gestation.<sup>7</sup> The abstract does not permit consideration of the study's design or findings in any depth or detail. Therefore, we are unable to draw any conclusions about the study's methodological merit or its findings.

In conclusion, FDA finds that there is insufficient scientific support for a claim that use of terbutaline administered by continuous, subcutaneous infusion pump results in improved preterm labor treatment outcomes.

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<sup>5</sup>K.G. Perry et al., "Incidence of Cardiopulmonary Effects With Low-Dose Continuous Terbutaline Infusion," *American Journal of Obstetrics and Gynecology*, 173:1273-1277, 1995.

<sup>6</sup>K.D. Wenstrom et al., "A Placebo Controlled Randomized Trial of the Terbutaline Pump for Prevention of Preterm Delivery," *American Journal of Perinatology*, 14(3):87-91, 1997.

<sup>7</sup>F. Lam et al., "Pregnancy Prolongation and Route of Tocolytic Administration in Patients With Singleton Gestation," *American Journal of Obstetrics and Gynecology*, 178:180, 1998.

## 2. Safety

You cite numerous articles from the medical literature describing the side effects and toxicities known to be associated with subcutaneously administered terbutaline and other beta-agonists. FDA reviewed each of these articles during its consideration of the citizen petition regarding subcutaneous terbutaline submitted in 1996 by the National Women's Health Network (NWHN) (96P-0258/CP1) and in drafting the November 1997 "Dear Colleague" letter. Estimates of specific event frequencies vary across studies, but their qualitative nature is highly consistent over nearly two decades of research and across dosing modalities.

You state that metabolic and cardiovascular effects of terbutaline have generally been found to be dose related and more commonly seen with the intravenous form of terbutaline (Petition at 6). You also state that with prudent fluid management and dosing, administration of beta-mimetics for tocolysis appears to be safer and to produce fewer undesirable side effects (*id.*). FDA agrees that excess fluid administration has been identified as a risk factor for pulmonary edema in patients receiving terbutaline. However, pulmonary edema has been shown to occur even with carefully managed hydration.

You cite the 1995 study by Perry et al. as evidence of the better safety profile of subcutaneous terbutaline (Petition at 7, 14). However, as discussed above, the authors do not specify their criteria for chart selection in this retrospective chart review, creating a significant potential for bias in outcome determination. Interestingly, the overall spectrum of toxicity reported in the Perry study is the same as in all other studies of terbutaline. Patient predictors of these events are not uniformly reliable, which is an important reason why in-hospital administration of parenteral terbutaline is often prescribed.

Evaluating the safety of subcutaneous terbutaline in the management of preterm labor is hampered by a lack of targeted clinical pharmacology data on such use. However, while actual administered doses (in milligrams) of terbutaline are lower in the subcutaneous form than in the oral form, the achievable systemic drug levels are quite similar, with maximum concentrations achieved faster subcutaneously. Because of the high bioavailability of subcutaneously administered terbutaline, subcutaneous doses repeated at close intervals can lead to systemic levels that rapidly approach those typical of intravenous terbutaline tocolysis. Because of these higher systemic drug levels and their known associated toxicities, it is generally agreed that intravenous terbutaline administration requires in-hospital monitoring. FDA is concerned that physicians and patients may be falsely reassured that smaller doses of terbutaline administered at close intervals by subcutaneous infusion pose a reduced safety risk, when just the opposite may be true.

Published reports on the use of continuous, subcutaneous terbutaline cite incidences of pulmonary edema, cardiac arrhythmia, tachycardia, diaphoresis, extreme tremors, hypertension, and other

known toxicities and side effects of the drug.<sup>8</sup> However, no attempt has been made to compare incidences of adverse events in a prospective, randomized study. The reports describe a variety of dosing strategies, with no standardization or attempt to correlate dosing with the known pharmacokinetics and pharmacodynamic activity of the drug. Such correlations are critical to ensuring the safety of any drug administered parentally in an outpatient setting.

You cite several references describing maternal deaths associated with administration of beta-mimetic tocolytic therapy and state that thirteen maternal deaths have been reported to FDA in patients using terbutaline sulfate for tocolysis (Petition at 6). You further attempt to compare data estimating the use of ritodrine and terbutaline in women during pregnancy and to extrapolate maternal mortality rates for each drug on this basis (*id.* at 7).

Estimates of this type are unreliable for a number of reasons. One is that the reporting rate to manufacturers or FDA for adverse events of marketed drug products is generally agreed to be less than 10 percent even under the best of circumstances. Reporting may be even less likely when the treating provider or healthcare facility has a fear of potential legal liability, as may be the case with off-label administration of terbutaline for tocolysis. In addition, estimates of off-label use of terbutaline for tocolysis are far less reliable than those of ritodrine for tocolysis, which is its sole labeled indication.

In summary, FDA finds no scientifically sound data to support the contention that subcutaneously administered terbutaline is less toxic than intravenous or oral terbutaline. In fact, subcutaneous dosing is likely to result in blood levels of terbutaline that are equivalent to or higher than blood levels achieved with oral doses of the drug and that may approach those of intravenous administration in some instances. Because the relationships between terbutaline dose, plasma levels, tocolytic efficacy, and toxicity are not well characterized, careful monitoring of patients who receive the drug, even on a short-term basis (up to 72 hours), is imperative.

### C. Regulatory Status of Tocolytics in the United States

You correctly state that FDA has approved only one drug, ritodrine hydrochloride, for use as a tocolytic (Petition at 15). You cite the 1992 advisory committee review as the reason for the sponsor's withdrawal from the market of the oral formulation of that drug (*id.*). The advisory committee concluded that oral ritodrine as maintenance tocolytic therapy had no place in the

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<sup>8</sup>See, e.g., D.L. Levy, "Morbidity Caused by Terbutaline Infusion Pump Therapy," *American Journal of Obstetrics and Gynecology*, 170:1835, 1995; J.R. Fischer and B.L. Kaatz, "Continuous Subcutaneous Infusion of Terbutaline for Suppression of Preterm Labor," *Clinical Pharmacy*, 10:292-296, 1991; P.G. Quinn et al., "Terbutaline Hepatitis in Pregnancy," *American Journal of Gastroenterology*, 89:781-784, 1994; D.R. Hudgens and S.E. Conradi, "Sudden Death Associated With Terbutaline Sulfate Administration," *American Journal of Obstetrics and Gynecology*, 169:120-121, 1993; K.J. Moise et al., "Continuous Subcutaneous Infusion Pump Therapy for Premature Labor: Safety and Efficacy," *Southern Medical Journal*, 85:255-260, 1992.

management of obstetric patients at the currently recommended dose and that it could not attain such status without further study of dosing. As you note, the sponsor subsequently decided to withdraw its oral ritodrine product from the market rather than conduct additional studies. Although some may regard that as unfortunate, it was FDA's responsibility to provide the data on the drug's effectiveness to the advisory committee.

You point out that terbutaline, along with other commonly prescribed beta-mimetic tocolytics, has been approved for use in many countries outside the United States (Petition at 15). Of the other beta-mimetics, hexoprenaline sulfate was reviewed in 1990 by the Fertility and Maternal Health Advisory Committee, which unanimously recommended that it be approved. This drug has not been marketed in the United States for reasons unrelated to the clinical data in the NDA for the drug. Most recently, FDA reviewed an application for the oxytocin antagonist, atosiban. At a meeting of the Reproductive Health Drugs Advisory Committee on April 20, 1998, the committee unanimously agreed that atosiban had not been established as safe and effective in the treatment of preterm labor and recommended that it not be approved for marketing. The advisory committee also recommended certain clinical trial endpoints for the sponsor to use in conducting further trials.

You state that "an environment exists in the United States which makes it difficult for manufacturers to gain FDA approval for drugs used in pregnancy" (Petition at 15). FDA strongly disagrees. It is imperative that FDA make regulatory decisions with the input of experienced, knowledgeable clinicians engaged in the practice of medicine and in research related to regulated products. FDA's advisory committee system is specifically designed to provide for presentation of scientific and regulatory issues to such experts, allowing them to offer advice to the Agency in an open public forum. FDA's regulatory decisions on tocolytics generally have been consistent with advisory committee recommendations and the scientific data underlying applications for approval of tocolytics. Like all sponsors seeking marketing approval, sponsors of tocolytic drugs must overcome the challenges inherent in conducting clinical trials and demonstrating the safety and effectiveness of their products. The existence of such challenges does not justify lowering the standard of evidence for demonstrating the safety and effectiveness of new drugs that is required by law and that physicians and patients expect. The Reproductive Health Drugs Advisory Committee recognized this at its April 20, 1998, meeting in recommending that FDA require trials of tocolytics to demonstrate at least some benefit to infants of mothers who receive the drug.

#### **D. FDA Actions Regarding Terbutaline**

You state that since the May 1993 advisory committee meeting, FDA has convened no further advisory or scientific panel meetings or discussions on the use of terbutaline in preterm labor. You maintain that since that meeting, several clinical studies have been published that address the safety and efficacy of "low dose" subcutaneous infusion of terbutaline as a tocolytic (Petition at 17-18). However, as discussed in Section I.B.1, these studies do not provide sufficient evidence

demonstrating that continuous, subcutaneous infusion of terbutaline is effective for managing preterm labor.

You contend that the November 13, 1997, "Dear Colleague" letter "came as a shock to the medical community" and others and that "FDA had apparently reversed its stance" on terbutaline since the 1993 advisory committee meeting (Petition at 18). FDA has not changed its policy regarding the tocolytic use of terbutaline. FDA believes, as it did in 1993, that the public literature suggests that terbutaline in general may be effective in preventing preterm labor for a brief period of perhaps 48 to 72 hours, but that evidence of long-term effectiveness is lacking. The Agency's decision to issue the "Dear Colleague" letter on the prolonged use of subcutaneous terbutaline via infusion pump for managing preterm labor was based on the Agency's concern about the widespread promotion of the use of terbutaline in a manner that has not been shown to be effective and that may not provide the margin of safety that most patients and physicians expect of a marketed drug product.

You express concern about FDA's purported "closed door" decisionmaking in issuing the "Dear Colleague" letter. You also maintain that some institutions have changed protocols and some insurance carriers have changed reimbursement patterns because of alleged "misinformation and resulting fear" caused by the letter. You call for an objective, scientific, and open discussion to understand FDA's intent in issuing the letter (Petition at 18-19).

FDA properly met its statutory and regulatory responsibilities in investigating and responding to the issues raised in the citizen petition submitted by the NWHN. As stated above, the Agency issued the "Dear Colleague" letter because it found no evidence that subcutaneous terbutaline was effective for long-term use in prolonging pregnancy and because the published literature raised significant safety concerns about such use. FDA remains concerned about the use of continuous, subcutaneous terbutaline for managing preterm labor for the reasons discussed in Section I.B.2. The Agency also believes that the active promotion of subcutaneous administration of terbutaline falsely assures healthcare providers and patients that subcutaneous terbutaline is safe and effective for prolonging pregnancy.

FDA looks forward to the availability of data from contemporaneously controlled trials on the safety and effectiveness of prolonged subcutaneous administration of terbutaline as a tocolytic. FDA will work with any party interested in designing such a clinical trial. If data from such studies become available, FDA will give serious consideration to convening an advisory committee meeting to provide a forum for public discussion of the data.

## **II. ACTIONS REQUESTED IN THE PETITION**

You request that FDA take several specific actions regarding the use of terbutaline for managing preterm labor (Petition at 2). Following are the Agency's responses to your requests.

**A. That FDA Reevaluate the Position Expressed in the “Dear Colleague” Letter**

This request is granted. FDA has reevaluated its position in great depth since the issuance of the November 13, 1997, “Dear Colleague” letter. As discussed above, FDA has reviewed the published data on the safety and effectiveness of terbutaline for managing preterm labor, including the more recent studies you cite in the petition. Having conducted this review, the Agency reiterates its position, as set forth in the “Dear Colleague” letter, that terbutaline administered intravenously appears to be effective for an initial, brief (approximately 48 to 72 hours) period of tocolysis, but that there is no evidence of a benefit from prolonged treatment with any form of terbutaline, including subcutaneous administration. Moreover, the published literature on the effectiveness of subcutaneous terbutaline remains confined to observational studies, generally without the benefit of randomization or contemporary controls.

**B. That FDA Notify the Recipients of the “Dear Colleague” Letter That (1) Terbutaline Is as Safe and Effective as Ritodrine, (2) No New Warning Statements Have Been Added to Terbutaline Labeling for Over Ten Years, and (3) the Deaths of Patients Receiving Terbutaline Have Not Been Confirmed to Be Due to Terbutaline**

This request is denied. FDA approved a ritodrine hydrochloride injection product for tocolysis; the Agency has not approved any form of terbutaline for tocolysis. Moreover, as stated above, FDA is unaware of any studies warranting a change in the Agency’s position (stated in the “Dear Colleague” letter) questioning the safety and effectiveness of continuous, subcutaneous terbutaline for managing preterm labor. Consequently, the Agency sees no reason to issue another “Dear Colleague” letter at this time.

**C. That FDA Acknowledge That It Has Restricted Physician Choices for Prescribing Tocolytic Therapy by Issuing the “Dear Colleague” Letter**

This request is denied. As discussed above, FDA has taken no action that would prohibit the use of any form of terbutaline by physicians in the practice of medicine, including treating preterm labor. FDA has received a number of inquiries from third-party payers regarding the “Dear Colleague” letter. Each party has assured the Agency that decisions regarding payment for subcutaneous terbutaline use with home uterine monitoring are made by the company’s own medical experts and not on the basis of such a letter from FDA.

**D. That FDA Acknowledge That It Has Placed Unwarranted Liability on Physicians Prescribing Subcutaneous Terbutaline Maintenance Therapy**

FDA’s decision to issue the “Dear Colleague” letter was based on a concern that the prolonged, at-home use of subcutaneous terbutaline was being promoted for an indication for which there

was no evidence of sustained effectiveness and regarding which there were significant safety concerns. FDA acknowledges that its action may have raised concerns for physicians who prescribe terbutaline for off-label use. However, the Agency believes that issuance of the "Dear Colleague" letter was consistent with its responsibility to alert the public to important safety and efficacy concerns about marketed drug products.

**E. That FDA Ask Terbutaline Manufacturers to Remove Package Insert Statements on the Use of Terbutaline in Preterm Labor and to Submit Applications for Approval of Terbutaline for the Treatment and Prevention of Preterm Labor**

You request that FDA require the manufacturers of terbutaline (approved for use as a bronchodilator) to remove the labeling statements (appearing in the PRECAUTIONS and WARNINGS sections of package inserts) against the use of terbutaline for managing preterm labor. (The PRECAUTIONS section of the package inserts for Novartis' Brethine products states that "terbutaline sulfate should not be used for tocolysis"; the WARNINGS section of the inserts for Hoechst Marion Roussel's Bricanyl products states that the products are "not indicated and should not be used for the management of preterm labor.") As noted in Section I.A, FDA has worked with the manufacturers of terbutaline to address the need for clarification and characterization of the uses and risks of terbutaline. FDA remains willing to review a supplemental application for a tocolytic indication for terbutaline as well as revisions to terbutaline labeling concerning use in managing preterm labor. However, the Agency has no basis at this time to require terbutaline manufacturers to remove statements about tocolysis from package inserts.

**F. That FDA Expedite the Review of Any Pending Applications for Approval of Tocolytic Drugs**

You ask that FDA grant accelerated or fast-track review to new drugs for the treatment and prevention of preterm labor. Please be assured that FDA is keenly aware of the need for safe and effective tocolytic agents. The Agency has worked intensively with sponsors who seek to develop new tocolytics and will continue to do so. Moreover, we will strongly consider granting priority review status to any NDA that we receive for a tocolytic agent.

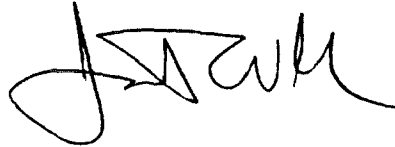
**III. CONCLUSION**

Having again reviewed the published literature on terbutaline, FDA finds nothing that warrants changing the position stated in its November 1997 "Dear Colleague" letter that continuous, subcutaneous administration of terbutaline for preterm labor has not been demonstrated to be effective and is potentially dangerous. However, the Agency would be willing to review any new data from clinical studies on subcutaneous terbutaline that may become available.

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Therefore, for the reasons stated above, FDA denies the requests set forth in your petition except as specified otherwise.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'J. Woodcock', with a large, stylized initial 'J'.

Janet Woodcock, M.D.

Director

Center for Drug Evaluation and Research